

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date  
27 January 2005 (27.01.2005)

PCT

(10) International Publication Number  
WO 2005/007603 A2

(51) International Patent Classification?: C07C 43/00

(21) International Application Number: PCT/IT2004/000375

(22) International Filing Date: 6 July 2004 (06.07.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 0316910.9 18 July 2003 (18.07.2003) GB

(71) Applicant (for all designated States except US): SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.p.A. [IT/IT]; Viale Shakespeare, 47, I-00144 Roma (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): GIANNINI, Giuseppe [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.p. A., Via Pontina, Km. 30,400, I-00040 Pomezia (IT). MARZI, Mauro [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.p. A., Via Pontina, Km. 30,400, I-00040 Pomezia (IT). ALLOATTI, Domenico [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.p. A., Via Pontina, Km. 30,400, I-00040 Pomezia (IT).

(52) S.p. A., Via Pontina, Km. 30,400, I-00040 Pomezia (IT). TINTI, Maria, Ornella [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.p. A., Via Pontina, Km. 30,400, I-00040 Pomezia (IT). RICCIANI, Teresa [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.p. A., Via Pontina, Km. 30,400, I-00040 Pomezia (IT). MARCELLINI, Marcella [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.p. A., Via Pontina, Km. 30,400, I-00040 Pomezia (IT).

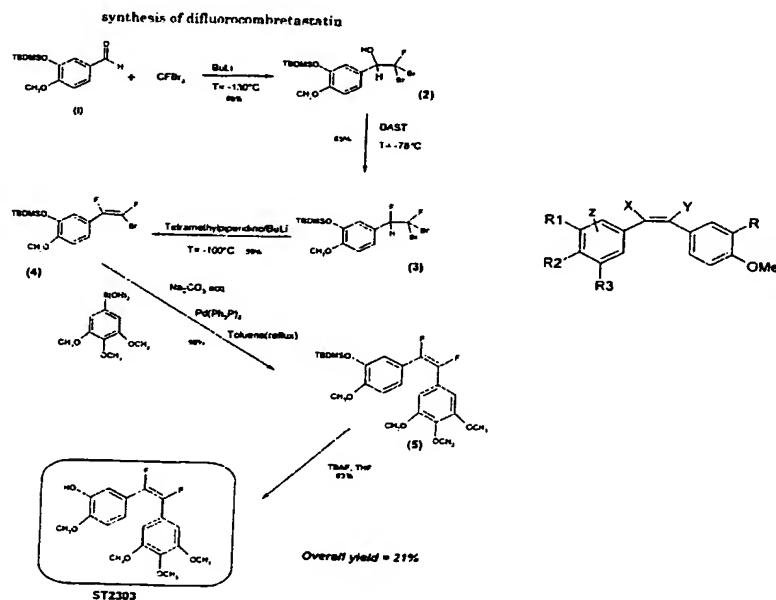
(74) Agents: SPADARO, Marco et al.; Cavattoni - Raimondi, Viale dei Parioli, 160, I-00197 Roma (IT).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH,

[Continued on next page]

## (54) Title: FLUOROCOMBRETASTATIN AND DERIVATIVES THEREOF



(57) Abstract: The present invention is related to new derivatives of Combretastatin, of Formula (I) obtained by total synthesis. The strategy developed for each of the compounds is to i) replace a halogen (i.e. fluorine atom) to hydrogen on olefinic bound; ii) replace an aromatic ring in a natural product with an amino-aromatic ring. Said compounds recognize and bind the tubulin site: are useful for treating pathological states which arise from or are exacerbated by cell proliferation - as anticancer and/or antiangiogenic activity, in a mammal - to pharmaceutical compositions comprising these compounds.



GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

BEST AVAILABLE COPY